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Risk of Cardiac Events in Family Members of Patients With Long QT Syndrome

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Objectives. **This study sought to identify risk factors for cardiac events (syncope, aborted cardiac arrest or sudden cardiac death) in family members of patients with the long QT syndrome.**

Background. **Patients with the long QT syndrome are known to be at high risk for cardiac events. Whenever the first member of a family is identified as having the long QT syndrome (proband), there is concern regarding the likelihood of cardiac events in other family members.**

Methods. **A multivariate logistic regression model was used to evaluate the risk of cardiac events in 637 family members who were first- and second-degree relatives of 151 probands with the long QT syndrome and in a subset of 513 family members who were not receiving beta-adrenergic blocking agents. There were 293 first-degree (46%) and 344 second-degree relatives (54%) (293 men [46%], 344 women [54%]). Fifty percent of the family members had a corrected QT interval (QTc) >0.44 s, and relative tachycardia and bradycardia were observed in 12% and 25%, respectively.**

Results. **The risk of cardiac events occurring before age 40 in family members not taking beta-blockers was influenced by the QTc interval (odds ratio [OR] 1.18/0.01 increase in QTc value; 95% confidence interval [CI] 1.12 to 1.24), relative tachycardia (OR 2.21, 95% CI 0.97 to 5.02) or bradycardia (OR 2.24, 95% CI 1.10 to 4.56) and an interaction term combining gender and closeness of the relationship to the proband (OR for female first-degree relative 3.23 vs. all second-degree relatives, 95% CI 1.67–6.22).**

Conclusions. **Female first-degree relatives of patients with the long QT syndrome have a higher risk of cardiac events than male first- or second-degree relatives, independent of recorded electrocardiographic findings. Not only bradycardia, but also tachycardia increases risk of cardiac events in family members of patients with the long QT syndrome.**

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Primary QT prolongation is frequently associated with a propensity to ventricular arrhythmias, syncope and sudden arrhythmic death (1–4). The earliest clinical observations of patients affected with the long QT syndrome, reported by Jervell and Lange-Nielsen (5) in 1957 and afterward by Romano et al. (6) in 1963 and Ward (7) in 1964, suggested a strong familial pattern to this disorder. Recent reports (8–10) further demonstrated that idiopathic long QT syndrome has a complex and heterogeneous pattern of gene linkage. The genetic background of the disease indicates that whenever the first member of a family (proband) is identified as having the long QT syndrome, there is an increased risk of cardiac events (syncope, cardiac arrest or cardiac death) in family members of the proband. It is unclear what clinical and electrocardiographic (ECG) variables might be meaningfully used to estimate an increased likelihood of cardiac events in the family members of patients with the long QT syndrome. The present study evaluates the incidence and risk of cardiac events in family members of probands with the long QT syndrome and provides a clinically useful model for risk assessment.

Methods

Study group and follow-up. The enrollment of families with long QT syndrome in the International Long QT Syndrome Registry has previously been described (11,12). Since 1979, patients with suspected long QT syndrome who were referred to the internationally dispersed investigators were considered for enrollment in the registry. On the basis of a clinical history of syncope or cardiac arrest or a family history of unexplained syncope or sudden cardiac death and evident prolongation >0.44 s of the QT interval corrected for heart rate (QTc) (according to Bazett's formula [13]), an identified patient with the long QT syndrome was enrolled in the registry as a proband. Thereafter, family members (siblings, children, parents, aunts, uncles, grandparents and grandchildren) of

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each proband with the long QT syndrome were contacted and enrolled in the registry, with 12-lead ECG results analyzed, if available. Yearly follow-up information, with particular emphasis on cardiac events, was obtained for each relative whenever possible.

To evaluate the risk of cardiac events (syncope, cardiac arrest or cardiac death) in 3,263 family members of 301 probands with the long QT syndrome, the following assumptions were made in selecting a study group for the present analysis: 1) In view of the suspected hereditary mechanism of the long QT syndrome, the present study focused on 2,275 family members (the base study population) who were the most likely to be affected by the disorder, that is, the first- and second-degree relatives of the 180 probands who had evident prolongation of repolarization (QTc ≥0.46 s). 2) Prior analyses (1,3,12) showed that cardiac events usually occur in patients with the long QT syndrome at a young age. To avoid a potentially confounding influence of ischemic heart disease (more frequent in older age), the analysis was limited to the family members with a first cardiac event before age 40 and to family members who reached age 40 without experiencing a cardiac event. 3) To identify simultaneously both clinical and ECG risk factors in a multivariate logistic regression model, the final group was limited to subjects with available ECGs. Therefore, the subjects selected for inclusion in this analysis were those with an available ECG who had not experienced a cardiac event by age 40 (at least 40-year follow-up from the date of birth) and those who had a documented cardiac event before age 40 (follow-up from the date of birth to the date of the first cardiac event). This approach resulted in analysis of the risk of cardiac events in 637 family members from 151 probands with the long QT syndrome.

Clinical and ECG variables. Clinical and ECG variables usually available when a patient with suspected long QT syndrome is evaluated were studied. Preselected variables recorded in the registry included the following data for family members: gender, relation to the proband (first- or second-degree relative), QTc and RR interval values and data on the related proband (QTc interval and age of proband at first event). The QT and RR intervals were measured in lead II. The QT interval was measured from the beginning of the Q wave to the end of the T wave, defined as the point of return of the T wave to baseline, while excluding the U wave. The observed QT interval was corrected for heart rate according to Bazett's formula (13).

Age adjustment for the RR interval (heart rate) was applied in the family members studied (14). Primarily, a regression analysis was done using age (for those <16 years old), heart rate and squared deviation of heart rate from its mean value. The quadratic term was significant. Because quadratic terms are difficult to interpret and use in clinical conditions, we chose a percentile approach to simplify presentation and interpretation. On the basis of 1,185 ECGs reviewed from the base population of family members of patients with the long QT syndrome, five categories for heart rate (dividing at 10th, 25th, 75th and 90th percentiles) were originally used. Because patients with the adjacent heart rate categories (below the 10th percentile and between the 10th and 25th percentiles, and between the 25th and 75th and 75th and 90th percentiles) showed essentially identical odds ratios for cardiac events, we finally pooled them into three categories: below the 25th percentile, 25th to 90th percentiles and above the 90th percentile with respective terms of relative bradycardia, normal heart rate and relative tachycardia. The terms *relative tachycardia* and *relative bradycardia* are used because the observed cutoff points are somewhat different from the usual ECG definitions of tachycardia and bradycardia. Relative tachycardia (above the 90th percentile) and relative bradycardia (below the 25th percentile) were defined according to the following heart rates: for age <2 years, >150 beats/min and <110 beats/min, respectively; for age 2 to <5 years, >120 beats/min and <95 beats/min, respectively; for age 5 to <10 years, >110 beats/min and <75 beats/min, respectively; and for age ≥10 years, >85 beats/min and <60 beats/min, respectively.

Statistical analysis. Comparisons of baseline clinical and ECG variables between family members with and without cardiac events were performed using *t* tests for continuous variables and chi-square tests for dichotomous variables. In the selected 637 family members, a stepwise regression analysis was used to choose clinical variables (those with $p < 0.05$) for inclusion in the final multivariate logistic regression model designated to determine an association between pertinent clinical and ECG variables and risk of cardiac events. After the selection of a tentative model, interaction terms were considered. Because some of the patients studied were treated with beta-blockers, the multivariate logistic analysis was also performed for those not receiving beta-blockers. Estimates of relative risks in a Cox proportional hazards model were not performed because in a number of family members, information on type or date of events and ECG results were missing. The ECG results were known for 1,185 subjects only. The percentage of people with missing ECG results was 46% for those without and 9% for those with cardiac events before age 40. A multivariate analysis including ECG information and using Cox regression would not be valid and would lead to substantially biased estimates of the hazard ratios and survival curves. Cumulative cardiac event rates over time were described only for variables (gender and relationship to proband) available in the entire base population of 2,275 family members by Kaplan-Meier curves (15) with a log-rank test used to evaluate differences between curves.

Results

Clinical characteristics of family members. The clinical characteristics of the base population of 2,275 family members and of the 637 family members selected for risk analysis were similar (Table 1). These two groups were derived from probands who had equally prolonged QTc intervals (0.531 ± 0.059 s [mean ± SD]) and a similar age at first cardiac event. Approximately 50% of family members were female. The numbers of first- and second-degree relatives of the probands were well balanced; 46% were first-degree relatives. The

Table 1. Clinical Characteristics of Family Members of Probands With Long QT Syndrome

	Base Population (n = 2,275)*	Subjects Selected for Risk Analysis† (n = 637)
Family members		
Female	1,123 (49%)	344 (54%)
Male	1,152 (51%)	293 (46%)
1st-degree relative	875 (38%)	293 (46%)
Female	446 (20%)	160 (25%)
Male	429 (19%)	133 (21%)
2nd-degree relative	1,400 (62%)	344 (54%)
Female	677 (29%)	184 (29%)
Male	723 (32%)	160 (25%)
QTc interval (s)		
Mean	0.444 ± 0.045	0.446 ± 0.043
>0.44–0.46	218 (18%)	133 (21%)
>0.46–0.50	219 (18%)	124 (19%)
>0.50	116 (10%)	66 (10%)
Mean heart rate (beats/min)	71 ± 15	67 ± 12
Relative tachycardia‡	107 (9%)	75 (12%)
Relative bradycardia‡	284 (24%)	160 (25%)
Probands (no.)	180	151
Mean QTc interval (s)	0.531 ± 0.059	0.531 ± 0.059
Mean age at 1st event (yr)	16 ± 12	14 ± 10

*Electrocardiographic data available for 1,185 family members. †See Methods for description of selection from base population. ‡See Methods for definition. Unless otherwise indicated, data presented are mean value ± SD or number (%) of subjects. QTc interval = corrected QT interval.

gender distributions among first- and second-degree relatives were also similar. Fifty percent of family members had a QTc interval >0.44 s, and 10% presented with marked prolongation of repolarization (QTc interval >0.50 s). Relative tachycardia and bradycardia, defined from the base population of 1,185 family members with available ECG results, were exhibited by a similar proportion of family members who qualified for the risk stratification model (75 with relative tachycardia [12%], 160 with relative bradycardia [25%]). Of 637 family members analyzed in a risk stratification model, 124 were treated with beta-blockers (20%). The clinical characteristics of the remaining 513 subjects (no beta-blockers) were remarkably similar to those of the 2,275 and 637 family member groups. These data confirm that the cohort chosen for the final risk evaluation had clinical and ECG characteristics representative of the entire base population of first- and second-degree relatives of probands.

Cardiac events (syncope, cardiac arrest or cardiac death) occurred in 109 (17%) of 637 family members. More cardiac events occurred in patients treated with beta-blockers (57 [46%] of 124) than in the untreated group (52 [10%] of 513) because many of these patients were enrolled in the international registry after beta-blocker therapy had been started, frequently for a previous cardiac event. The total number of cardiac events in the base population is uncertain because information on the occurrence, type or date of events was missing for 222 of them. Among the 2,053 subjects with available data, cardiac events were documented in 120 (6%).

Prognostic significance of gender and relationship to the proband. A higher incidence of cardiac events in female than in male family members was observed in the base population of 2,053 family members (7% vs. 4%, respectively, p = 0.012) and was further confirmed in the selected 637 family members (20% vs. 13%, respectively, p = 0.020). However, as shown in Figure 1, this gender-related difference in cardiac events was seen mainly in adults; in children (<18 years old), cardiac event rates were similar for boys and girls. The closeness of the relationship to the proband with the long QT syndrome also had a significant influence on the likelihood of events during

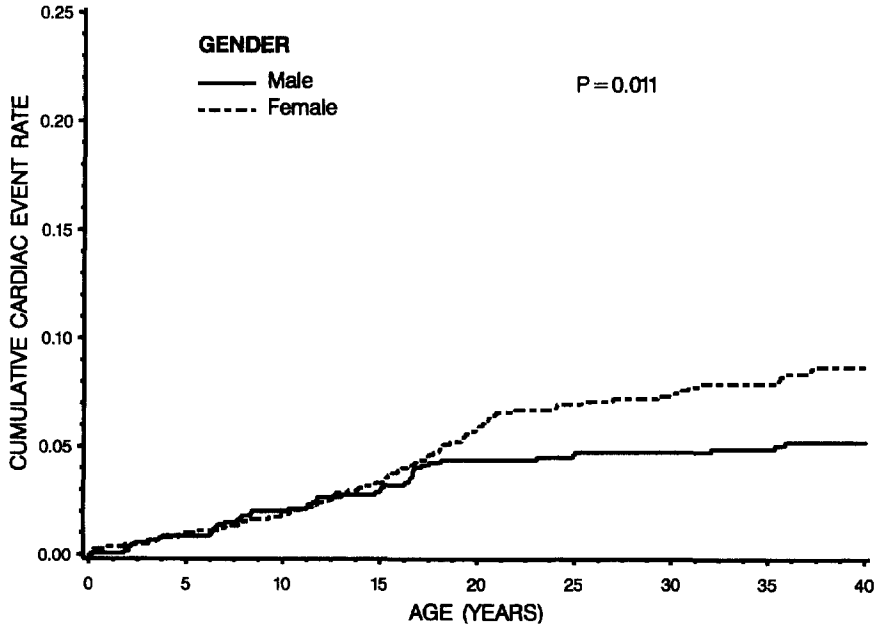

Figure 1. Cumulative cardiac event rates in 1,041 male and 1,012 female family members of probands with the long QT syndrome.

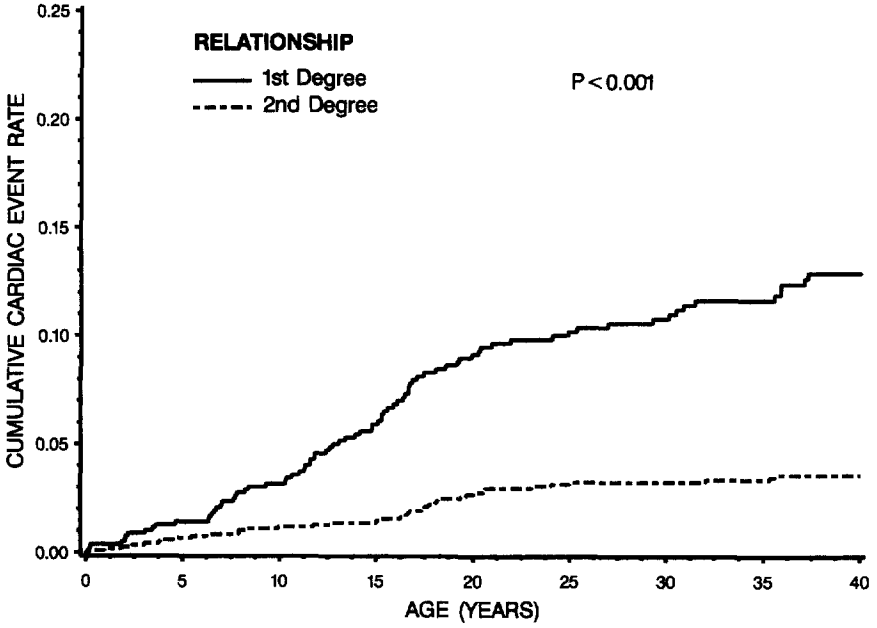

Figure 2. Cumulative cardiac event rates in 808 first-degree and 1,245 second-degree relatives of probands with the long QT syndrome.

follow-up (Fig. 2). First-degree relatives of probands exhibited a significantly higher incidence of cardiac events than second-degree relatives (10% vs. 3%, respectively, of the base population of 2,053 family members, $p < 0.001$; 26% vs. 10%, respectively, of the selected 637 subjects, $p < 0.001$). Simultaneous analysis of gender and relationship to the proband confirmed a statistically significant ($p < 0.001$) interaction between these factors, with first-degree female relatives of the proband having the highest rate of cardiac events (Fig. 3). Male and female second-degree relatives had a similar risk of cardiac events that was independent of age.

Electrocardiographic predictors of cardiac events. Duration of repolarization was significantly longer in family members with than without a cardiac event (mean QTc interval 0.47 ± 0.05 vs. 0.44 ± 0.04 s, respectively, $p < 0.001$). The QTc duration was a strong and significant predictor of cardiac events (Fig. 4), with increased QTc values associated with a significant increase in the risk of cardiac events. The odds ratio of 1.18/0.01 increase in QTc value (95% confidence interval [CI] 1.12 to 1.24, $p < 0.001$) translates to a practical understanding that a family member with a QTc interval of 0.50 s would have a likelihood of cardiac events five times greater than a family member with a QTc interval of 0.40 s ($1.18^{10} = 5.2$).

Family members with a cardiac event during follow-up had a mean heart rate similar to those without an event (67 ± 12 vs.

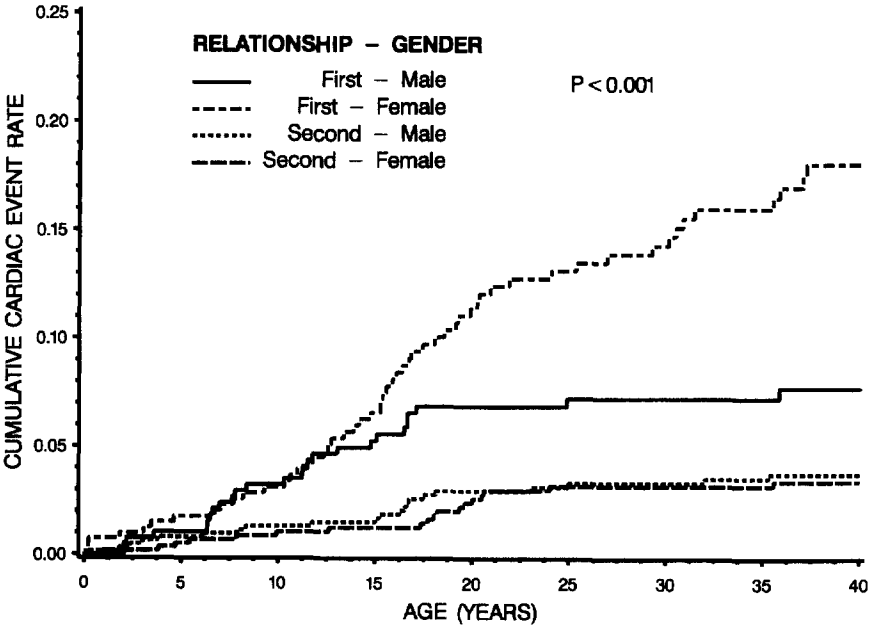

Figure 3. Cumulative cardiac event rates in relation to gender and relationship to proband interaction (400 first-degree male, 408 first-degree female, 641 second-degree male and 604 second-degree female relatives).

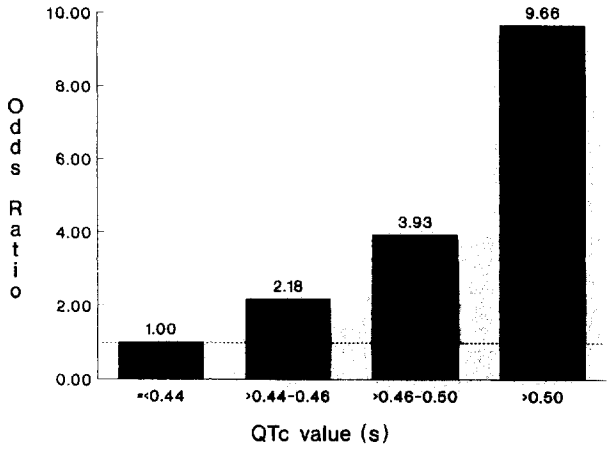

Figure 4. Odds ratios of cardiac events in relation to QTc interval duration in 637 family members of probands with the long QT syndrome (univariate analysis).

67 ± 13 beats/min, respectively). Despite a similar mean heart rate, there was a significant association between cardiac event rate and heart rate. Figure 5 shows a bimodal pattern of this relation, with either relative bradycardia or tachycardia associated with augmented risk of cardiac events. This complex relation was confirmed by a logistic regression analysis when continuous age-adjusted values of the RR interval and its square (RR^2) were both used as predictors (both RR and RR^2 had statistically significant [$p < 0.05$] association with cardiac events).

Multivariate risk of cardiac events in family members of patients with the long QT syndrome. The prognostic value of the clinical and ECG variables was analyzed in two risk stratification models (Table 2): *model 1* = 637 family members (including 124 taking beta-blockers); *model 2* = 513 family members (excluding the 124 taking beta-blockers). The subset of 124 patients taking beta-blockers was not studied separately because this group was not representative of the study population of family members. Both multivariate models (Table 2) confirmed the prognostic importance of repolarization duration, with a gradually elevated risk for cardiac events with increasing QTc values. The relative tachycardia and bradycardia, recorded on the screening ECG, provided additional information about elevated risk for cardiac events in family members of patients with the long QT syndrome, independent of QTc prolongation (the interaction terms were not significant). A similar risk of cardiac events in male and female second-degree relatives was observed in the base population (Fig. 3); for this reason, in the multivariate logistic regression models we compared male or female first-degree relatives with second-degree relatives independently of their gender. Female first-degree relatives had a statistically significant increase in risk of cardiac events. There was no significant influence of the proband's QTc interval or age at first event on the occurrence of cardiac events in family members. The mean QTc value and age in related probands was similar in family members with and without cardiac events.

Figure 5. Odds ratios of cardiac events in relation to heart rate (see Methods) in 637 family members of probands with the long QT syndrome (univariate analysis).

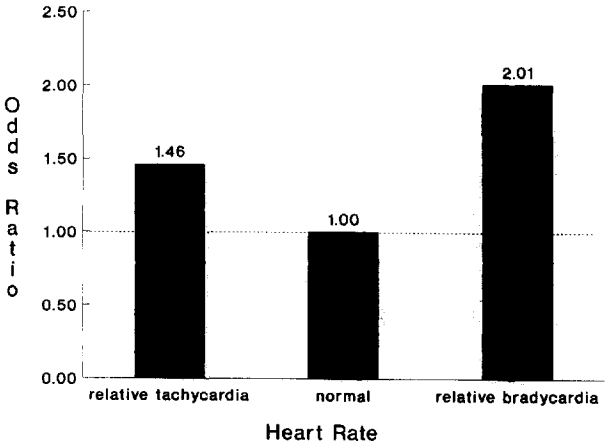

Table 2. Risk Stratification of Family Members of Probands With Long QT Syndrome

	Predictive Model 1 (637 family members; 109 cardiac events)		Predictive Model 2 (513 family members without beta-blockers; 52 cardiac events)	
	OR (95% CI)	p Value	OR (95% CI)	p Value
QTc interval (s)				
>0.44–0.46	2.11 (1.11–4.01)	0.023	1.43 (0.62–3.31)	0.401
>0.46–0.50	3.87 (2.11–7.09)	<0.001	2.42 (1.08–5.42)	0.032
>0.50	9.69 (4.97–18.93)	<0.001	4.84 (1.95–12.02)	<0.001
Relative tachycardia*	1.48 (0.76–2.90)	0.248	2.21 (0.97–5.02)	0.059
Relative bradycardia*	2.04 (1.21–3.45)	0.008	2.24 (1.10–4.56)	0.026
1st-degree relative				
Male	1.65 (0.89–3.07)	0.114	0.87 (0.33–2.28)	0.775
Female	4.06 (2.42–6.80)	<0.001	3.23 (1.67–6.22)	<0.001

*See Methods for definition of age-adjusted relative tachycardia and bradycardia. CI = 95% confidence interval; OR = odds ratio (for all corrected QT intervals [QTc] vs. QTc intervals <0.44 s; for relative tachycardia or bradycardia vs. normal heart rate; for female or male first-degree relative vs. second-degree relative [either gender]).

Discussion

Importance of clinical decision in family members. In the present study, the diagnosis of the long QT syndrome in 180 probands led to the screening of >2,000 first- and second-degree family members. In the probands, a prior cardiac event was a strong predictor of further events during follow-up (11,12). However, in family members the frequency of cardiac events is much lower, and other clinical factors should be considered when evaluating patient risk for a future event. In the current study, we evaluated clinical and ECG variables readily available during the physician's first contact with family

members of patients with the long QT syndrome. The pertinent factors included gender, relationship to the proband, proband's "severity" (defined by a history of cardiac events and QTc length) and standard ECG variables (QTc interval and heart rate values).

Gender and relation to proband. The present study extends the earlier observations (11,12) that female family members have a higher risk than male members. However, this pattern was not consistent for all age categories. As shown in Figure 1, the curves for men and women do not diverge until age 17 (or until age 10 in a group without beta-blocker treatment). This age-related association recalls the pattern of QTc values in normal men and women (16). Below age 15 years, QTc values are similar in boys and girls; thereafter, women tend to have longer QTc intervals than men (16). Nevertheless, the multivariate risk model indicates that women, especially first-degree relatives, have an increased risk of experiencing a cardiac event up to age 40 years compared with men, and this risk is independent of QTc interval (Table 2). These findings demonstrate that when both female and male family members have the same QTc value, the risk of cardiac events is greater in female than male relatives.

In the current study, we found a significant association between the closeness of the relation to the proband and the risk of a cardiac event in family members. The observation of a higher risk in the first- than in second-degree relatives of probands with the long QT syndrome further highlights the hereditary aspect of this disorder. The relationship to the proband is even stronger than female gender as a predictor of cardiac events in family members of patients with the long QT syndrome. The association between relation to the proband and risk for cardiac events is not age dependent.

QTc length as a strong predictor of cardiac events. The duration of repolarization (QTc interval) was the strongest independent predictor of subsequent cardiac events in family members of probands with the long QT syndrome. As expected, the pattern of this association followed previous observations made in probands (11,12). The remarkably high risk for cardiac events was associated with QTc prolongation >0.50 s, a value observed in 10% of family members studied. The incidence of cardiac events in this selected group was as high as 30% to 45%, further suggesting that these patients should be considered candidates for treatment. The need for prophylactic therapy in family members with a borderline prolonged QTc interval (0.44 to 0.46 s) is questionable. Because long QT syndrome gene carriers may also present with normal or borderline QTc values (17), additional factors such as gender, relation to the proband and other ECG variables, such as T wave alternans (18) or dispersion of repolarization (19), may be useful in identifying an increased risk for cardiac events.

Bimodal pattern of risk related to heart rate. An increased heart rate was reported to be an independent risk factor in probands with the long QT syndrome (odds ratio 1.018/1 beat/min increase in heart rate, $p < 0.01$) but was not a significant predictor of cardiac events in family members (12). In the current analysis, we observed a bimodal relation between the risk of cardiac events and heart rate in family members of patients with the long QT syndrome. Both relative tachycardia and bradycardia were associated with an increased risk of cardiac events. A separate logistic regression model, with continuous values of RR and RR^2 included, also yielded a statistically significant curvilinear association between cardiac events and heart rate. However, clinical interpretation of quadratic terms in risk stratification models is impractical; thus, we used simpler age-adjusted criteria to define relative tachycardia and bradycardia in our study population. The proposed marginal values are not entirely analogous to the traditional definitions of tachycardia and bradycardia, but they delineate an increased risk for cardiac events in family members of patients with the long QT syndrome. The bimodal pattern of cardiac event risk related to heart rate carries an important therapeutic implication, suggesting that optimization of heart rate should be considered whenever antiadrenergic (beta-blocker or left cardiac sympathetic denervation, or both) or pacemaker therapy is introduced. In support of this concept, the independent risk for cardiac events related to relative tachycardia (Table 2) was higher in the group not treated with beta-blockers than in the group that included the 124 treated patients (OR 2.21 and 1.48, respectively).

Risk stratification and therapy in family members of patients with the long QT syndrome. The protective effect of beta-blockers in patients with symptomatic long QT syndrome has been reported (11,20,21), but decisions regarding prophylactic treatment in patients with the long QT syndrome without a history of cardiac events remains controversial. The findings from the present study provide important information regarding the decision to use prophylactic treatment with beta-blockers in asymptomatic family members of patients with the long QT syndrome. First-degree relatives with marked prolongation of repolarization (QTc interval >0.50 s), with a tendency to develop tachycardia, particularly if they are female, should be considered candidates for beta-blocker treatment. The probability of cardiac events in such family members is significantly increased compared with that in second-degree men with a QTc interval ≤0.50 s and a normal heart rate. Because ~10% of family members of patients with the long QT syndrome present with significant bradycardia, and because beta-blocker therapy may contribute to or exacerbate the bradycardia, pacemaker therapy should be considered in this high risk subset, especially if symptomatic (22,23). In view of our observations, a pacing rate should be programmed not only to protect against critical bradycardia, but also to maintain a normal age-adjusted heart rate. Left cardiac sympathetic denervation is reserved for selected high risk symptomatic patients with the long QT syndrome (24,25), and the factors discussed in the present risk stratification model may have little (if any) influence on this therapeutic decision.

Study limitations. The limitations of the present study relate to the observational character of the Long QT Syndrome Registry. Missing data on the occurrence and time of cardiac events and lack of recorded ECGs in several family members

made analysis of all enrolled subjects impossible. The final analysis of 637 family members of patients with long QT syndrome could cause a selection bias because these family members all had complete clinical and ECG records. The presence of complete ECG data in these subjects could imply that they are at higher risk for cardiac events. The subset of 124 of these family members who received beta-blockers also constitutes a high risk group because such treatment is usually considered for patients with evident long QT syndrome symptomatology. Nevertheless, we believe that the results of the multivariate logistic regression analyses are reasonably representative for all our family members of patients with the long QT syndrome because of the similarities in overall clinical characteristics between the base and selected (with and without beta-blockers) populations (Table 1).

Clinical implications. The present study indicates that readily available clinical and ECG variables are useful for estimating the risk for cardiac events in family members of patients with the long QT syndrome. The factors evaluated (gender, relationship to the proband and QTc and heart rate values) could also be used to develop a therapeutic algorithm in the management of family members of patients with long QT syndrome. An additional implication of the present study relates to the description of the long QT syndrome phenotype. Our observations on the association between cardiac events and relation to the proband, heart rate and gender further emphasize the complex nature of this disease process.

References

1. Moss AJ, Schwartz PJ. Delayed repolarization (QT and Q-U prolongation) and malignant ventricular arrhythmias. Mod Concepts Cardiovasc Dis 1982;51:85–90.
2. Moss AJ. Prolonged QT syndromes. JAMA 1986;256:2985–7.
3. Garson A Jr, Macdonald D, Fournier A, et al. The long QT syndrome in children. An international study of 287 patients. Circulation 1993;87:1866–72.
4. Schwartz PJ, Moss AJ, Vincent GM, Crampton RS. Diagnostic criteria for the long QT syndrome. An update. Circulation 1993;88:782–4.
5. Jervell A, Lange-Nielsen F. Congenital deaf-mutism, functional heart disease with prolongation of the QT interval, and sudden death. Am Heart J 1957;54:59–68.
6. Romano C, Gemme G, Pongiglione R. Aritmie cardiache rare dell'eta' pediatrica. II. Accessi sincopali per fibrillazione ventricolare parossistica. Clin Pediat (Bologna) 1963;45:656–83.
7. Ward OC. A new familial cardiac syndrome in children. J Ir Med Assoc 1964;54:103–6.
8. Keating M, Atkinson D, Dunn C, Timothy K, Vincent GM, Leppert M. Linkage of a cardiac arrhythmia, the long QT syndrome, and the Harvey ras-1 gene. Science 1991;252:704–6.
9. Benhorin J, Kalman YM, Medina A, et al. Evidence for genetic heterogeneity in the long QT syndrome. Science 1993;260:1960–1962.
10. Moss AJ. Molecular genetics and ventricular arrhythmias. N Engl J Med 1992;327:885–7.
11. Moss AJ, Schwartz PJ, Crampton RS, Locati E, Carleen E. The long QT syndrome: a prospective international study. Circulation 1985;71:17–21.
12. Moss AJ, Schwartz PJ, Crampton RS, et al. Long QT syndrome. Prospective longitudinal study of 328 families. Circulation 1991;84:1136–1144.
13. Bazett HC. An analysis of the time relations of electrocardiograms. Heart 1920;7:353–67.
14. Garson A Jr. The Electrocardiogram of Infants and Children: A Systematic Approach. Philadelphia: Lea & Febiger, 1983:396.
15. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–81.
16. Rautaharju PM, Zhou SH, Wong S, et al. Sex differences in the evolution of the electrocardiographic QT interval with age. Can J Cardiol 1992;8:690–95.
17. Vincent GM, Timothy KW, Leppert M, Keating M. The spectrum of symptoms and QT intervals in carriers of the gene for the long-QT syndrome. N Engl J Med 1992;327:846–852.
18. Zareba W, Moss AJ, le Cessie S, Hall WJ. T wave alternans in idiopathic long QT syndrome. J Am Coll Cardiol 1994;23:1541–6.
19. Priori SG, Napolitano C, Diehl L, Schwartz PJ. Dispersion of the QT interval. A marker of therapeutic efficacy in the idiopathic long QT syndrome. Circulation 1994;89:1681–1689.
20. Schwartz PJ, Periti M, Malliani A. The long QT syndrome. Am Heart J 1975;89:378–390.
21. Schwartz PJ, Locati E. The idiopathic long QT syndrome. Pathogenetic mechanisms and therapy. Eur Heart J 1985;6 Suppl D:103–114.
22. Eldar M, Griffin JC, Abbott JA, et al. Permanent cardiac pacing in patients with the long QT syndrome. J Am Coll Cardiol 1987;10:600–607.
23. Moss AJ, Liu JE, Gottlieb S, Locati EH, Schwartz PJ, Robinson JL. Efficacy of permanent pacing in the management of high-risk patients with Long QT Syndrome. Circulation 1991;84:1524–1529.
24. Moss AJ, McDonald J. Unilateral cervicothoracic sympathetic ganglionectomy for the treatment of long QT interval syndrome. N Engl J Med 1971;285:903–4.
25. Schwartz PJ, Locati EH, Moss AJ, Crampton RS, Trazzi R, Ruberti U. Left cardiac sympathetic denervation in the therapy of congenital long QT syndrome. A worldwide report. Circulation 1991;84:503–11.